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EXAMINER
SCHNIZER, R

1806/0615

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| ART UNIT | PAPER NUMBER |
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| 1806 | 11 |

DATE MAILED: 06/15/93

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

**Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:**

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☒ Notice re Patent Drawing, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

**Part II SUMMARY OF ACTION**

1. ☒ Claims 1-11 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-11 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

15. Formal drawings have been submitted which fail to comply with 37 CFR 1.84. Please see the enclosed form PTO-948.

16. Applicant is reminded of the proper content of an Abstract of the Disclosure.

A patent abstract is a concise statement of the technical disclosure of the patent and should include that which is new in the art to which the invention pertains.

If the patent is of a basic nature, the entire technical disclosure may be new in the art, and the abstract should be directed to the entire disclosure.

If the patent is in the nature of an improvement in an old apparatus, process, product, or composition, the abstract should include the technical disclosure of the improvement.

In certain patents, particularly those for compounds and compositions, wherein the process for making and/or the use thereof are not obvious, the abstract should set forth a process for making and/or use thereof.

If the new technical disclosure involves modifications or alternatives, the abstract should mention by way of example the preferred modification or alternative.

The abstract should not refer to purported merits or speculative applications of the invention and should not compare the invention with the prior art.

Where applicable, the abstract should include the following: (1) if a machine or apparatus, its organization and operation; (2) if an article, its method of making; (3) if a chemical compound, its identity and use; (4) if a mixture, its ingredients; (5) if a process, the steps. Extensive mechanical and design details of apparatus should not be given.

The instant abstract refers to speculative applications of the claimed invention. The efficacy of the instant invention for the in vivo treatment of B cell lymphomas in humans is not supported in the specification.

17. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of

the invention and failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure and failing to present the best mode contemplated by the applicant for carrying out the invention.

A) It is apparent that the transfectoma comprising anti-CD20 in TCAE 8 is required to practice the instant invention as claimed in the specification and cited in the claims. The claims of the instant invention read on the aforementioned monoclonal antibody. As a required element, the transfectoma producing the aforementioned antibody must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If said antibodies are not so obtainable or available, the enablement requirements of 35 U.S.C. 112, first paragraph, may be satisfied by a deposit of the instant transfectoma. See 37 CFR 1.802.

The specification does not provide a repeatable method for obtaining the instant antibodies and it does not appear to be a readily available material. Deposit of the transfectoma producing the aforementioned antibodies would satisfy the enablement requirements of 35 U.S.C. 112.

If a deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made under the terms of the Budapest Treaty and that all restrictions imposed by the depositor on the availability of the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. See 37 CFR 1.808.

If a deposit is not made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made at an acceptable depository and that the following criteria have been met:

a) during the pendency of the application, access to the deposit will be afforded to one determined by the Commissioner to be entitled thereto;

b) all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent;

c) the deposit will be maintained for a term of at least thirty years and at least five years after the most recent request for the furnishing of a sample of the deposited material;

d) a viability statement in accordance with the provisions of 37 CFR 1.807; and

e) the deposit will be replaced should it become necessary due to inviability, contamination or loss of capability to function

in the manner described in the specification.

In addition, the identifying information set forth in 37 CFR 1.809 (d) should be added to the specification. See 37 CFR 1.803-1.809 for additional explanation of these requirements.

B) Applicant has not demonstrated the relevance of the instant experimental data in cynomolgus monkeys to treating disease in humans. Applicant needs to establish that the cynomolgus monkey is an art recognized model for human disease and that experimental data generated in this model has relevance to human disease. Therefore the specification is not enabling for the instant invention.

C) Applicant has not demonstrated that the instant invention can be used to deplete B cells per se. Applicant has demonstrated that the instant invention can be used to deplete normal B cells from blood, lymph nodes and bone marrow, with varying degrees of efficacy depending on the dosage of antibody administered. However applicant has provided no information with regards to splenic B cells or CD5 positive B cells which do not necessarily reside in the aforementioned anatomical locations. Therefore the specification is not enabling for the instant invention.

D) Applicant has not demonstrated that the instant invention can be used to treat B cell lymphoma. Tumor cells are distinct from normal cells in a wide variety of physiological parameters. Applicant has not demonstrated that the depletion of normal B cells in vivo would apriori mean that B cell lymphoma cells so treated would react in a similar fashion. Therefore the specification is not enabling for the instant invention.

E) Applicant has not demonstrated that the instant invention can be used to treat a B cell disorder in vivo. Therefore the specification is not enabling for the instant invention.

18. Claims 1-11 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

19. Claims 1-10 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 6 are indefinite in the recitation of "B cell disorders" because it is unclear what this encompasses.

20. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this

section made in this Office action:

> A person shall be entitled to a patent unless --
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

21. Claim 11 is rejected under 35 U.S.C. § 102(a) as being clearly anticipated by Anderson et al.

Anderson et al. teach the chimeric monoclonal antibody of the instant invention( see entire document).

22. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

23. Claim 11 is rejected under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Liu et al.

Liu et al. teach an anti-CD20 humanized chimeric antibody with human gamma 1 and kappa constant regions( see page 3521, second column, *Materials and Methods* section). Liu et al. teach that this monoclonal antibody is immunologically active( i.e. the antibody can mediate ADCC with human effectors and complement

dependent cytotoxicity with human complement)( see abstract, page 3521). The only apparent difference between the two antibodies is the ATCC deposit number of the instant antibody, which is merely a particular designation bestowed upon deposit of an antibody with the ATCC. Since the Patent Office does not have the facilities for examining and comparing the instant antibody to that antibody taught in the prior art, the burden is on applicant to show an unobvious distinction between the instant antibody and the antibody of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430(CCPA 1977).

24. Claims 1-10 are rejected under 35 U.S.C. § 103 as being unpatentable over Liu et al. in view of Press et al.

The claims are drawn to treatment of B cell disorders with a humanized chimeric anti-CD20 monoclonal antibody. Liu et al. teach the humanized chimeric anti-CD20 monoclonal antibody of the instant invention(see paragraph 23). Liu et al teach that the use of humanized chimeric anti-CD20 monoclonal antibody would have advantages over murine anti-CD20 monoclonal antibodies in immunotherapy because the chimeric antibody has much higher ADCC activity than the murine antibody, and has a longer circulation time in vivo(see page 3526, first paragraph). Liu et al also teach that the humanized chimeric anti-CD20 monoclonal antibody fixes human complement more effectively than murine anti-CD20 antibody(see abstract, page 3521). Liu et al. do not use their humanized chimeric anti-CD20 monoclonal antibody in vivo for immunotherapy. Press et al. teach in vivo immunotherapy of human B cell lymphomas (a B cell disorder)with a murine anti-CD20 monoclonal antibody(see entire document). It would have been prima facie obvious to one of ordinary skill in the art to have treated a B cell disorder in vivo with a humanized chimeric anti-CD20 monoclonal antibody because Press et al. teach the use of murine anti-CD20 monoclonal antibody in vivo for the therapy of human B cell lymphoma, while Liu et al. teaches the humanized chimeric anti-CD20 monoclonal antibody and its potential advantages over murine anti-CD20 monoclonal antibody in the in vivo therapy of human B cell tumors. With regards to the doses of antibody cited in the claims, applicant teaches in page 12 of the specification, line 12 that, "The skilled artisan is readily credited with assessing a particular patient and determining a suitable dosage that falls within the ranges (cited in the specification and claims), or if necessary, outside of the ranges". This routineer would have also derived the temporal sequence of antibody administration described in the claims. One of ordinary skill in the art would have been motivated to do the aforementioned in order to develop the most therapeutically efficacious treatment for human B cell tumors. One of ordinary skill in the art would have a reasonable expectation of success because Press et al. teach the immunotherapy of human B cell lymphoma using a murine anti-CD20 monoclonal antibody, and Liu

et al. teach a humanized chimeric anti-CD20 monoclonal antibody, and the advantages of using this antibody over a murine anti-CD20 monoclonal antibody in immunotherapy.

25. No claim is allowed.

26. Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CMI Fax Center telephone number is (703) 308-4227.

27. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ron Schwadron whose telephone number is (703) 308-4680. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 180 receptionist whose telephone number is (703) 308-0196.

Ron Schwadron

Ron Schwadron, Ph.D.
June 9, 1993

Christina Chan

Y. CHRISTINA CHAN
PRIMARY EXAMINER
GROUP 180
ORE Unit 1806